

Remarks / Arguments

This supplemental response is provided to add the declaration of Gunther Neuhaus in support of a finding of non-obviousness. For brevity, this supplement does not provide a duplicate of arguments set forth in the pending response. As such, the response to Office Action filed 6/2009 is incorporated herein by reference.

Response to Rejection Under 35 U.S.C. § 103(a) (Obviousness)

I.

Claims 1-3 and 17 Are Not Obvious over Reutter et al In View of Lee et al.

Claims 1-3 and 17 stand rejected under 35 U.S.C. § 103(a) as being obvious over Reutter et al. (1996, Plant Tiss. Cult. Biotechnol. 1:142-147) in view of Lee et al. (US 6,020,169).

The examiner argues Reutter et al. teach growth of *P. patens* protonema transformed with a nucleic acid encoding a heterologous protein in a bioreactor culture and that the protonema produced large amounts of heterologous protein. The examiner acknowledges Reutter et al. do not disclose isolation of the protein from culture medium.

The examiner then cites Lee et al. as teaching isolation of biologically active heterologous protein from tobacco cells grown in suspension culture. The cells were transformed with a nucleic acid encoding Mab HC operably linked to a mammalian secretion signal peptide. The Mab HC was selectively secreted into the medium.

The examiner concludes the present invention is obvious because at the time of the invention it would have been obvious to modify the method of producing heterologous protein in *P. patens* protonema as taught by Reutter et al., to use a signal peptide in the transformation construct and isolate the protein from media as described in Lee et al.

A. Standard for Obviousness

A proper obviousness rejection requires consideration of the factual inquiries provided in Graham v. John Deere Co., 38 U.S. 1, 148 USPQ 459 (1966), including: 1) determining the scope and contents of the prior art; 2) ascertaining the differences between the prior art and the claims at issue; 3) resolving the level of ordinary skill in the pertinent art; and 4) considering the objective evidence of nonobviousness. Although Graham v. John Deere requires that certain factual inquiries be conducted to support a determination of the issue of obviousness, the actual determination of the issue requires an elevation in light of the findings in those inquiries as to the obviousness *of the claimed invention as a whole*, not merely the differences between the claimed invention and the prior art. Lear Siegel, Inc. v. Aeroquip Corp., 221 USPQ 1025, 1033 (Fed. Cir. 1984). Further, the teachings of a prior art reference are underlying factual questions in the obviousness inquiry. Para-Ordnance Mfg., Inc. v. SGS Imp. Int'l, Inc. 73 F.3d 1085, 1088 (Fed. Cir. 1995). Still further, a reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. In re Gurley, 27 F.3d 551, 553 (Fed. Cir. 1994). Accordingly, one can not use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention. In re Fritch, 23 USPQ2d 1780, 1784 (Fed. Cir 1992).

B. With respect to all claims, the present invention is not obvious over Reutter et al. in view of Lee et al. as further supported by the Declaration of Gunther Neuhaus

Applicants provide herewith a Declaration of Gunther Neuhaus (“Neuhaus Decl.”), an expert in the field of plant cultivation research and development, which attests to the significant differences between bryophytes or protonema tissue, vascular plants such as tobacco and specialized cell lines in suspension that are derived from tobacco, such as NT-1 and BY2 cells. Thus, the Neuhaus Decl. demonstrates one skilled in the art would not find the present invention obvious over Reutter et al. in view of Lee et al. and demonstrates the two areas of research would

not be reasonably combined to form the present invention.

Although Lee et al. provide a method of producing a polypeptide using a *Nicotiana tabacum*-clone 1 (NT-1) cell line transformed with a transgene, it would not be obvious to combine this with Reutter et al.'s whole organism approach to form the present invention. For instance referring to Neuhaus Decl para. 9,

“Although cell suspensions such as NT-1 cells and BY2 cells are useful in studying biological processes such as those that affect cell division, the cytoskeleton and hormone signaling, experiments directed towards the cell wall itself including its function, its protective characteristics or its role as a barrier are not considered reflective of cells within the intact plant. This is due in part to the manipulation of the cell during the culturing process to achieve its specialized characteristics.”

Manipulation of the plant cells to form specialized NT-1 and BY2 cells are discussed in Neuhaus Decl. paras. 11 and 12. The procedure begins by obtaining callus cells. The callus is then cultured over time. Importantly, even at this early step, the callus loses many characteristics associated with a plant cell from an intact plant, including loss of expression of photosynthetic genes and several metabolic genes. Neuhaus Decl. para 11. These specialized callus cells are considered “habituated plant cells.” Neuhaus Decl. para. 11.

However, specialization does not stop at the culturing of the callus. Instead the callus cells themselves are further manipulated to form a specialized cell suspension. Referring to para. 12,

“First, the callus has to be broken down in small mostly single cell aggregates which have to be cultured in a highly complex liquid culture medium including vitamins, sugars as well as plant hormones. Afterwards the cell suspension has to be subcultured every 8 to 10 days to ensure continuous cell division. Upon this subculturing procedure the cells have to be sieved, so that mostly only single cells or at least small cells serve as starting culture for the next growing cycle. If this is not done in the appropriate way the cells will die in the old suspension culture upon nutrient deficiency. In addition if the cell aggregates are grown too big they also will die as the inner cell mass will not get the required nutrients.”

Since cells are no longer in constant communication, the procedure itself can yield wide heterogeneity. This heterogeneity is addressed through further specialization. Thus, referring to

para. 13,

“Further culturing is performed to eliminate this heterogeneity. Thus, the specialized cell suspension is adapted for liquid culture conditions. Among the adaptations, especially with respect to homogeneity in “humidity” there is no need for a strong barrier i.e. rigid cell wall against the environment surrounding medium.”

Thus, as demonstrated in the attached declaration, the generation of specialized cells significantly affects the cell itself. Accordingly, while NT-1 cells are useful to study some cellular processes such as cell division, NT-1 cells are not considered to be a proper model for studying the cell wall in intact plants. Instead, as stated in Neuhaus Decl. para. 16,

“Instead, one would logically study whole intact tissue or a whole intact plant. Thus, a comparison between effects observed in a culture of suspended specialized cells would be difficult to transfer to an intact plant.”

Further, these differences are even more extreme when comparing a specialized cell suspension obtained from a vascular plant like tobacco with a non-vascular bryophyte, i.e. an intact protonema tissue. For instance, the classification difference itself between such bryophyte protonema and tobacco suggests there are important differences. Whereas tobacco plants include vascular tissue such as phloem, produce flowers and seeds, protonema tissue does not. When considering a comparison between a suspension of specialized cells from vascular plants like NT-1 and BY2 and protonema the comparison was deemed inadequate and the biological conclusion of no use. Neuhaus Decl. para. 19.

Further, the attached Neuhaus Decl. provides additional evidence that the two areas of research would not be reasonably combined to form the present invention. Specifically, given the approach chosen by the researcher the opposite path would not be useful in gaining additional insight. This is evident in a Neuhaus Decl. para 19, which concludes that results obtained from a cell suspension of specialized cells would not be useful when working with a culture of whole gametophyte tissue (like protonema); and results from a culture of whole gametophyte tissue (like protonema) would not be useful when working with a cell suspension of specialized sporophytic cells.

Thus, the Declaration of Gunther Neuhaus is further evidence that the present invention is not obvious over Reutter et al. in view of Lee et al. As such, applicants respectfully request the rejection be withdrawn and all claims allowed.

II.

Claims 1-3 and 17 Are Not Obvious over Reutter et al In View of Lee et al. and Further in View of Nasu et al.

Claims 1-3 and 17 stand rejected under 35 USC § 103(a) as being obvious over Reutter et al. (1996, Plant Tiss. Cult. Biotechnol. 1:142-147) in view of Lee et al. (US 6,020,169) further in view of Nasu et al (1997) J. Ferm. Bioengin. 58:519-523).

The examiner incorporates the discussion of Reutter et al in view of Lee et al as provided above and adds that Nasu et al. teach the transformation of *Marchantia polymorpha*, which is an auxotroph and thus its growth does not require sugars, vitamins or phytohormones.

The deficiencies of the rejection of Reutter et al in view of Lee et al. are discussed above. Nasu does not correct the deficiencies in the rejection. Broadly, Nasu involves the fixation of transformed cells in formaldehyde to assess intracellular expression of heterologous proteins and thus kills the cells.

Accordingly, claims 1-3 and 17 are not obvious over Reutter et al. in view of Lee et al. and further in view of Nasu et al. and applicant respectfully requests the rejection be withdrawn.

Conclusion

In view of the arguments set forth above, applicants respectfully request the rejections be withdrawn and the claims allowed.

Respectfully submitted,

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Date



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